Planned Parenthood®
Federation of America, Inc.

Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket number 200D-1350, "Draft Guidance for Industry on Labeling for Combined Oral Contraceptives"

Dear Sir/Madam:

Planned Parenthood Federation of America ("PPFA"), the nation's oldest and most trusted voluntary reproductive health care organization, submits respectfully these comments to "Draft Guidance for Industry on Labeling for Combined Oral Contraceptives." Each year, Planned Parenthood affiliates across the nation distribute millions of cycles of oral contraceptives (OCs) to the women who visit our clinics for family planning and other reproductive health care services.

As a network of clinicians whose primary focus is the delivery of family planning services and supplies, we appreciate fully the challenges inherent in developing labeling for combined oral contraceptives (COCs) that is meaningful to both practitioners and consumers. The overarching goal of this undertaking must be the communication of vital information that enables clinicians to make medically sound recommendations and women to make informed, educated decisions. Accordingly, we offer the comments below in the spirit of crafting the best possible labeling guidance.

Comments by Select Topics

Precautions – General (pg. 8, lines 286-292)

The draft guidance recommends that women using OCs have an annual history and physical examination, with specific reference to pelvic organs and cervical cytology. This recommendation, however, is not supported by the available medical literature and is inconsistent with the guidelines of leading national and international medical and health organizations. Indeed, the United States Agency for International Development,[1] the World Health Organization,[2] the International Planned Parenthood Federation,[3] the American College of Obstetricians and Gynecologists,[4] the Society of Obstetricians and Gynaecologists of Canada,[5] the Royal College of Obstetricians and Gynaecologists,[6] and the American Academy of Pediatrics[7] all conclude that pelvic examinations are not necessary prior to the initiation of OCs, even among adolescents.

Furthermore, if one looks at the Food and Drug Administration's (FDA) own OC/COC labeling documents, the evolution of thought vis-à-vis

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the decoupling of a pelvic examination from the initiation of OCs is readily apparent. The 1994 guidance states that, "the physical examination ... may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician."[8] This was later refined in the draft guidance made available in 2000: "Before initiating COC use, blood pressure should be measured and details of the woman's personal and family medical history should be obtained. Blood pressure should be measured periodically during COC use and additional clinical evaluation should be based on these initial and follow-up findings."[9]

Blood pressure assessment is the only portion of the recommended physical examination that is relevant to use of COCs. An annual physical examination with specific reference to the pelvic organs, as well as cervical cytology, is simply inconsistent with current medical practice. Women at low risk for cervical cancer with three prior negative screening tests for cervical dysplasia can reduce the frequency of their cervical cancer screening to every two to three years. The FDA's proposed labeling requirement, should it stand, would be at odds with current medical professional recommendations.

The statements of the aforementioned medical and health organizations, including the FDA, represent an evolution in both our understanding of hormonal contraceptives as well as the composition of the OCs themselves. When OCs were first available, it was prudent to require a physical examination, including a pelvic examination. As the body of medical and scientific literature grew and enhanced our understanding of hormonal contraceptives, and as the amount of hormone in each pill decreased, the necessity of a physical examination, and a pelvic examination in particular, was questioned. Eventually, medical and health organizations arrived at positions that decoupled the pelvic examination from initiation of OCs/COCs.

Additionally, as providers of family planning services, it has become apparent to us that the requirement of a pelvic examination prior to initiation of OCs/COCs often serves as barrier to contraception. Adolescents, in particular, are likely to avoid or delay initiation of contraception because of reluctance to undergo a pelvic examination. Because women's health is in no way compromised by delaying a pelvic examination when initiating OCs, PPFA believes that women are better served by eliminating this unnecessary requirement.

Finally, it is worth noting that Ortho Tri-Cyclen is also indicated for treatment of moderate acne vulgaris in females $\geq$ 15 years of age.[10] Women who are prescribed this COC for treatment of acne should certainly not be required to undergo a pelvic examination prior to initiation of treatment. Labeling that requires providers to perform a pelvic examination would be inconsistent with the use of this product for treatment of acne.

Given that there is no medical justification for requiring a pelvic examination prior to initiation of COCs, and that requiring such an examination has been shown to serve as a barrier to contraception, PPFA urges the FDA to reconsider its labeling guidance and omit the requirement for a pelvic examination from the final industry guidance document.

Indications and Usage (pg. 3, lines78-92) and How Well Does (OC Name) Work? (pgs. 13-14, lines 492-507)

PPFA believes that both the table directed at clinicians as well as the table indicated in the patient labeling section contain insufficient data to allow for informed choice. The informed choice process is a necessary and integral component of quality health care. In order to facilitate informed choice, complete and understandable information must be provided.

Furthermore, because the clinical trial data used to define the columns "Pregnancies Per 100 Women Per Year" (see table page 3, line 90) and "Number of Women Out of 100 Who Become Pregnant in 1 Year" (see table page 14, line 506) are derived from studies that are not comparable, retaining the data proposed in the June 2000 draft guidance is necessary. Finally, PPFA believes that the inclusion of "perfect use" data may increase women's compliance with their chosen method by motivating them to achieve maximum protection against unintended pregnancy.

The table below is one example of how the necessary data might be presented:

Method	% of Women Experiencing an Unintended Pregnancy within the First Year of Use*		Number of Women out of 100 who become pregnant in one year[3]
	Typical Use[1]	Perfect Use[2]	
No method[4]	85	85	
Spermicides[5]	29	15	25 or more
Withdrawal	27	4	
Periodic abstinence	25		
Calendar		9	
Ovulation method		3	
Sympto-thermal[6]		2	
Post-ovulation		1	
Cap[7]			
Parous women	32	26	
Nulliparous women	16	9	
Sponge			
Parous women	32	20	
Nulliparous women	16	9	
Diaphragm[7]	16	6	
Condom[8]			15
Male	15	2	
Female (Reality)	21	5	
Combined pill and minipill	8	0.3	
Evra patch	8	0.3	1
NuvaRing	8	0.3	
Depo-Provera	3	0.3	
IUD			
ParaGard (copper T)	0.8	0.6	Fewer than 1
Mirena (LNg IUS)	0.1	0.1	
Female sterilization	0.5	0.5	
Male sterilization	0.15	0.10	

More Pregnancies

Fewer Pregnancies

Lactational Amenorrhea Method: LAM is a highly effective, *temporary* method of contraception.[9]

Table Continued

*Source: Adapted from Trussell, J., "Contraceptive Efficacy," in R.A. Hatcher, J. Trussell, F. Stewart, W. Cates, G.K. Stewart, F. Guest, D. Kowal, 2004, *Contraceptive Technology: Eighteenth Revised Edition,* Irvington Publishers. On Press.

1 Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

2 Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

3 The estimates for drugs, condoms, diaphragms, and IUDs are derived from clinical trial data reviewed by the Food and Drug Administration. The estimates for sterilization and spermicides come from the medical literature. Source: Food and Drug Administration.

4 The percentages becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percentage who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

5 Foams, creams, gels, vaginal suppositories, and vaginal film.

6 Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.

7 With spermicidal cream or jelly.

8 Without spermicides.

9 However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

Precautions – Nursing Mothers (pg. 10, lines 386-391)

The 2004 draft guidance recommends that, if possible, nursing mothers be advised to use other forms of contraception until her child has been weaned. This recommendation differs significantly from the previously published draft guidance (2000), which states that, "women who are fully breast-feeding should not start taking COCs until 6 weeks postpartum."[11]

Although contraceptives containing both estrogen and progestin have been shown to reduce both the quantity and quality of breast milk, by delaying COC initiation until 6 weeks postpartum, sufficient time is allowed for establishing optimal breastfeeding techniques and skills. These techniques and skills, in turn, can mitigate against any decrease in milk quality or quantity that may result from COC initiation.

Absent medical evidence to the contrary, PPFA recommends that the FDA retain the earlier language that advises women to delay initiation of COCs until 6 weeks postpartum. This recommendation allows women who elect to contracept using COCs to protect themselves against an unintended pregnancy while continuing to breastfeed their

infants. Furthermore, this recommendation is supported by a World Health Organization study that found that infant growth was not affected by impaired milk secretion.[12]

Possible Health Benefits (pg. 11, lines 431-438)

PPFA believes that the list of non-contraceptive health benefits that accrue to pill users is too meager. The benefits indicated in the 2004 draft guidance relate specifically to menses and do not include the therapeutic implications of these benefits. The effects of consistent OC use on estrogen and progestin sensitive tissues and organs have been shown to result in non-contraceptive health benefits that form the basis for therapeutic uses of OCs in instances of dysfunctional uterine bleeding,[13] iron-deficiency anemia associated with menorrhagia,[14] hypothalamic amenorrhea with associated osteoporosis,[15] dysmenorrheal,[16] mittelschmerz,[17] polycystic ovarian syndrome,[18] acne,[19,20] and recurrent, functional ovarian cysts.[21] In addition, consistent use of COCs provides protection against pelvic inflammatory disease,[22,23] reduces the incidence and prevalence of benign breast disease,[24,25] and significantly reduces the lifetime risks of endometrial[26,27,28] and ovarian cancers.[29,30,31] Moreover, many women are attracted to the opportunity to delay menses when COCs are used continuously, without a hormone-free interval.[32]

How Do I Take (OC Name)? (pgs. 14-15, lines 508-537) and What Should I Do If I Miss Any Birth Control Pills? (pg. 15, lines 539-563)

The information provided in the most recent draft labeling guidance is insufficient and does not provide women with their full range of options with respect to initiating COCs. Oral contraceptives may be initiated at anytime during the woman's menstrual cycle, once it has been established that she is not pregnant.[33,34,35] This information, including the full range of options and explicit examples, should be conveyed. The guidance to "talk with your health care provider about when to start your birth control pill" should also be maintained.

In addition to expanding the options available to women regarding when to initiate COCs, an expanded discussion of the options available to women to ensure adequate contraceptive protection when one or more pills have been missed should also be included in this section.

PPFA recommends the following instructions regarding COC initiation for women who are neither postpartum nor post-abortion, and how to ensure adequate contraceptive protection when one or more pills have been missed:

> The first dose can be taken on any day, as long as pregnancy and recent unprotected intercourse are ruled out. If more than five (5) days have passed since the start of menstrual bleeding, use of back-up contraception

(such as condoms) is recommended for seven (7) days. For most women, a Sunday start translates into no menses on weekends.

- If a woman misses 1 pill, she should take it as soon as she remembers. If she does not remember until the next day, she should take 2 pills the next day, and complete the cycle pack.
- If a woman misses 2 consecutive pills, she should:
  - take 2 pills the day she remembers and 2 pills the following day, and complete the cycle pack; and
  - use a back-up method for 7 days.
- If a woman misses more than 2 consecutive pills, the risk of unplanned pregnancy may be substantial. She should:
  - stop taking the daily pills and use Emergency Contraception. Her period should begin within 2-3 weeks, unless she is pregnant;
  - begin a new package of pills on the Sunday after her period begins; and
  - use a back-up method of birth control (such as condoms) from the time the error was discovered until the 8th day of the new package of pills.

In addition, PPFA recommends that the FDA develop instructions for OC/COC initiation among women who are either postpartum or post-abortion.

Contraindications (pg. 4, lines 103-121)

Listed among the contraindications to COC use is "migraine with focal neurological symptoms." PPFA believes that this contraindication lacks specificity and should be refined to reflect current scientific findings regarding the association between migraine headaches and increased risk of ischemic stroke.

Specifically, the increased risk of ischemic stroke among women using COCs is found among those who experience "migraine with aura." The contraindication listed should therefore be migraine with aura - with aura defined as specific focal neurological symptoms which usually precede and resolve before onset of migraine headache.[36,37,38,39,40,41,42]

Approximately 70 percent of migraine sufferers experience migraine without aura. It is therefore crucial that the specific diagnosis of aura is accurately determined as those who experience migraine without aura are candidates for OCs. Aura's specific focal neurological deficits are primarily visual (99% of auras)[43] and are characterized by a bright spot which may increase in size to the shape of a letter "C" with development of scintillating edges that appear as "zigzags." These visual changes generally start centrally and then gradually spread laterally, with the size of the bright blind spot

increasing over a period of 5 to 60 minutes. Generally, the aura precedes and resolves before the onset of a migraine headache; occasionally, though, aura may occur without headache. Sensory or motor symptoms occur in association with one third of visual auras. When sensory motor symptoms occur they are usually unilateral in distribution, affecting one arm, the mouth and tongue, and rarely affecting the legs.[44]

Consistent with these data, the most recent update of the World Health Organization's *Medical Eligibility Criteria for Contraceptive Use, Third Edition* (in publication; http://www.who.int/reproductivehealth/publications/MEC_3/summary_tables.html), will reflect the terminology "migraine with aura" rather than "migraine with focal neurological symptoms."

PPFA further recommends that the Warnings section of the most recent draft guidance document (page 4, lines 123-134) indicate that COCs may be used in women experiencing migraine without aura, and who have risk factors for ischemic stroke (age 35 and older; diabetes mellitus, close family history of arterial disease under 45 years, hyperlipidemia, hypertension, obesity, and smoking) other than COC use.[45,46] Use of COCs among this population, however, should be cautious. To maintain consistency with the above recommendation, "Severe migraine headache" found on page 16, line 582, of the draft guidance should be changed to read "Migraine headaches with aura."

Drug Interactions: Anti-infective agents and anticonvulsants (pg. 8, lines 307-313) and What Else Should I Know About Taking (OC Name)? (pg. 17, lines 623-628)

As currently drafted, the language in this section is confusing. Providers and patients alike are left with the impression that most antibiotics, if not all, are contraindicated among COC users. The World Health Organization's *Medical Eligibility Criteria for Contraceptive Use, Third Edition* (in publication; http://www.who.int/reproductive-health/publications/MEC_3/ summary_tables.html), however, indicates that OCs are contraindicated only for users of rifampin and, in some cases, griseofulvin. There are no restrictions for use of COCs with other antibiotics. Unfortunately, the FDA's draft guidance is not clear on this point, particularly in the latter section referenced above.

PPFA suggests that the language be refined to clarify which specific antibiotics preclude use of COCs. Additionally, the revised language should make explicit the fact that antibiotics other than rifampin and griseofulvin are not contraindicated. Finally, this language should be reflected in both the package insert and the patient labeling.

Contraindications (pg. 4, line 108) and Who Should Not Take (OC Name)? (pg. 16, line 572)

PPFA recommends that the language found in the 2004 draft guidance regarding liver tumors and liver disease be changed to reflect the more accurate contraindication found in the 2000 draft guidance. Thus, the labeling guidance should read: "Liver tumors (benign and malignant), active liver disease."

Contraindications (pg. 4, line 109) and Who Should Not Take (OC Name)? (pg. 16, line 573)

Undiagnosed, abnormal genital bleeding is not a contraindication to either the initiation or continuation of COCs. While women who experience such bleeding should seek medical evaluation, undiagnosed, abnormal genital bleeding among women of reproductive age usually results from a benign and treatable condition. The COCs will not compromise the medical evaluation.

"Undiagnosed abnormal genital bleeding" should be deleted from the list of contraindications found on page 4 (line 109). Additionally, in order to maintain consistency throughout the document, line 573 (page 16), should also be deleted. The information contained in the Warnings section, Vaginal Bleeding Problems (page 7, lines 273-278) is sufficient and appropriate.

Contraindications (pg. 4, line 111)

PPFA recommends that the contraindication regarding thrombophlebitis or pulmonary embolism be replaced with the wording found in the 2000 draft guidance:

- Deep vein thrombosis (current or history)
- Pulmonary embolism (current or history)

Moreover, lines 110 and 115 (page 4) of the 2004 draft guidance should be replaced with specific information about genetic mutations such as homozygous factor V Leiden. Additionally, providers should be advised that routine screening for thrombophilic markers is not recommended.

PPFA therefore recommends that the contraindication be changed to: "Women with Known Thrombogenic Mutations (e.g. Factor V Leiden; Prothrombin mutation; Protein S; Protein C and Antithrombin deficiencies)."

Herbal Products (pg. 8, lines 324-328)

With the rising popularity of St. John's Wort, there now exists some evidence that women taking this product while using COCs may experience breakthrough bleeding. There is no evidence, however, that these same women are at risk for increased contraceptive failure. Given this lack of evidence, PPFA recommends that draft guidance be changed to reflect accurately the current body of knowledge. We suggest that lines 327-328 read as follows: ". . . p-glycoprotein transporter and may *result in breakthrough bleeding. To date, there is no evidence of increased oral contraceptive failure rates.*"[47]

Increased Cervical Ectopia (pg. 10, line 417)

There is no evidence to suggest that OCs/COCs increase a woman's risk for cervical ectopia (congenital displacement or malposition of any organ or part of the body). While there is evidence indicating that women on OCs may be at increased risk for developing increased cervical ectropion (a rolling outward or eversion of the margin of a part, i.e., eversion of endocervical glandular epithelium), this is not a pathological state and, in and of itself, cervical ectropion does not cause symptoms. Line 417 should therefore be deleted from the "Adverse Experiences" section of the draft guidance document.

Conclusion

Each year, thousands of health care providers prescribe millions of cycles of COCs to millions of women in the United States. It is imperative that the package insert and patient labeling that accompany each cycle of COCs be complete, accurate, and clear. Only then will providers be able to make sound medical recommendations and women be provided with the tools necessary to make informed decisions. As a highly trusted and leading provider of women's health care, PPFA is happy to provide you with our comments regarding the FDA's draft "Guidance for Industry – Labeling for Combined Oral Contraceptives." Our aim is simply to assist the FDA in its efforts to provide the most medically accurate and up-to-date information to women and their health care providers.

Sincerely,

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